Annual Congress of Epilepsy Society of Thailand
September 5th-6th, 2020

Role of Polytherapy in Drug Resistant Epilepsy

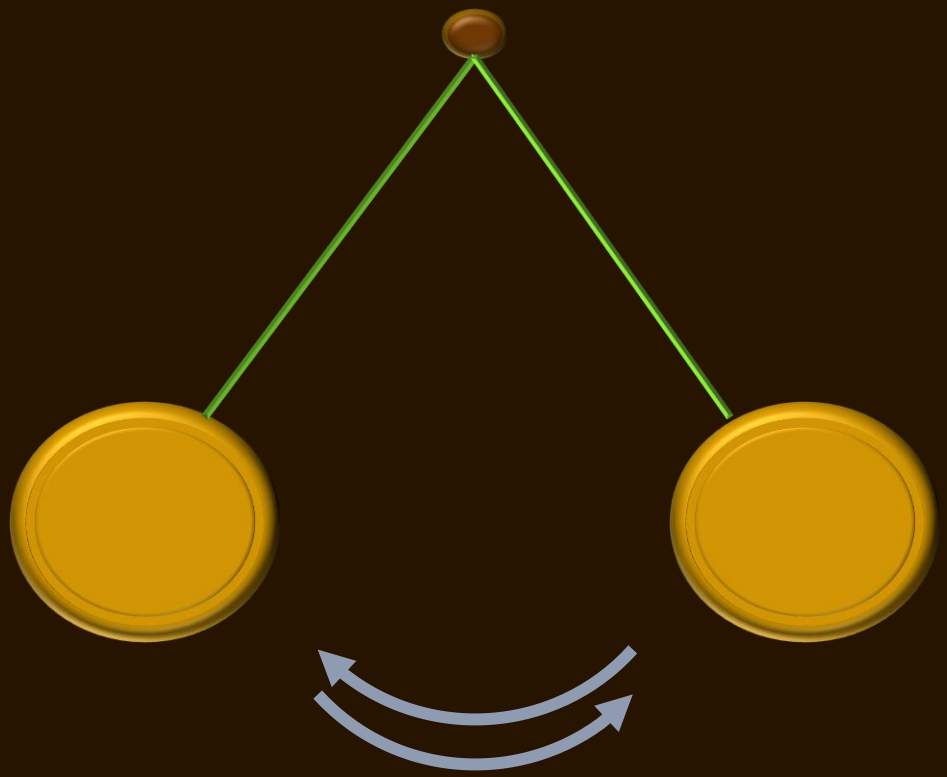
Byungin Lee, M.D.
Department of Neurology & Epilepsy Center
Inje University Haeundae Paik Hospital
Busan, KOREA

Role of Polytherapy in DRE

- SYNOPSIS -

- Era of Monotherapy
- New AEDs Era
- Polytherapy in Real World Practice

MODE of AEDs Therapy

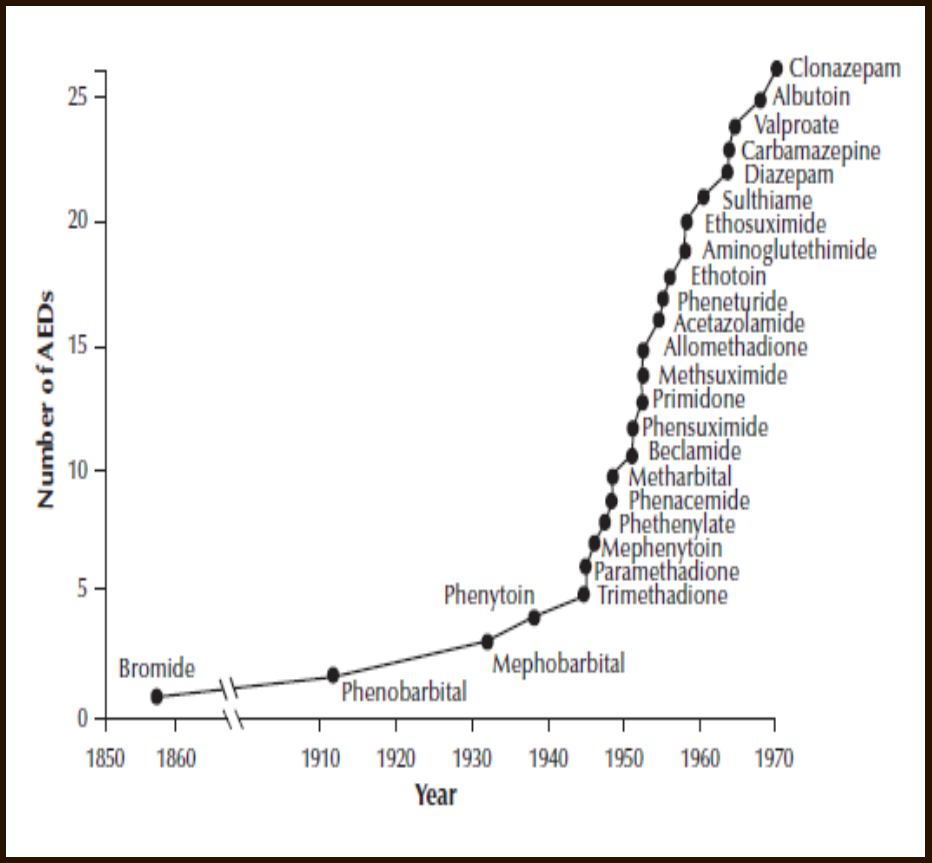


Monotherapy **VS.** **Polytherapy**

A full dose of one drug achieves better Sz control with fewer AEs.

Combination of AEDs of lower doses provide higher efficacy with less toxicities.

I. Era of Monotherapy
- introduction of AEDs -



From E Perucca, Epileptic Dis 2019

1989	Vigabatrin (Ireland and UK) Zonisamide (Japan and South Korea)
1990	Lamotrigine (Ireland) Oxcarbazepine (Denmark)
1993	Felbamate (US) Gabapentin (UK and US)
1995	Topiramate (UK)
1996	Fosphenytoin (US) Tiagabine (France)
1999	Levetiracetam (US)
2004	Pregabalin (EU and US)
2007	Rufinamide (EU) Stiripentol (EU)
2008	Lacosamide (EU and US)
2009	Eslicarbazepine acetate (EU)
2011	Retigabine (EU and US)*
2012	Perampanel (EU and US)
2016	Brivaracetam (EU and US)
2018	Cannabidiol (US)
2019	Cenobamate(US)

Hiatus (1970-1988): no introduction of New AEDs, but

1. Pharmacokinetics and drug interactions of AEDs
2. Spectrum of AEDs applicable to seizure types
3. Acute and chronic AEs of AEDs
4. RCTs of comparative Monotherapy

→ survival of only a few AEDs(PHT, CBZ, VPA, PB, ESM)

→ **MONOTHERAPY**

I. Era of Monotherapy

- **Before 1980, Polytherapy >>> Monotherapy**
  - A survey by Guelen et al. (1975) in early 1970's revealed that a patient took about 3 AEDs in average.

- **Introduction of blood level measurement in 1970's triggered the emergence of optimal monotherapy**
  - **Reynolds et al.** (Lancet 1976;1:923-926)
    - Among 31 Pts under PHT monotherapy, Szs were uncontrolled in 11 pts but 8 of them had subtherapeutic blood level.
  - **Shorvon and Reynolds** (BMJ 1979;2:1023-1025)
    - Trial of conversion to monotherapy in 40 pts under polytherapy
      - Successful conversion in 29 pts (72%) with Sz improvement in 16 pts (55%) and improvement of AEs in 16 pts (55%)

I. Era of Monotherapy

- Schmidt D (J N NS Psy 1982 and 1983)

SZ outcome	Add-on of 2nd drug (30 pts under max. monotherapy)	Conversion to monotherapy (36 pts under max. 2 drug therapy)
Sz improved	11 pts (37%)	13 pts (36%)
No change	12 pts (40%)	17 pts (47%)
Worse	7 pts (23%)	6 pts (17%)
AE	?	Total No of AEs: decreased No of pts with AEs: unchanged

- Schmidt and Richter (Ann Neurol 1986;16:85-87)

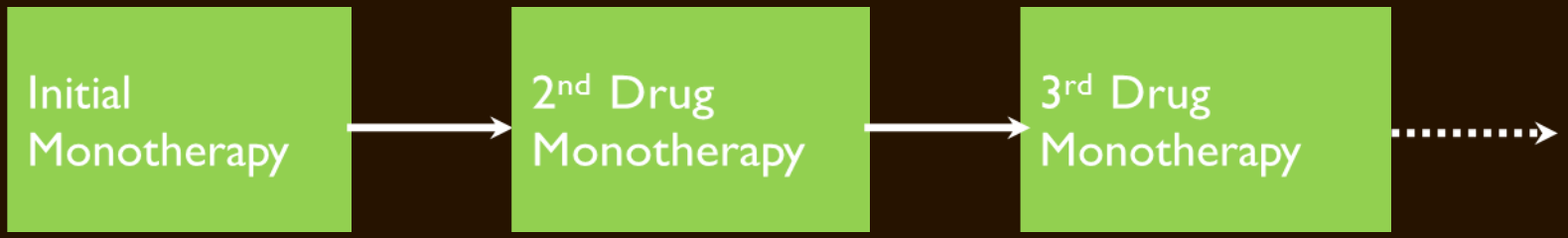
  Alterative monotherapy in 59 pts with refractory epilepsy:

  - ≥ 75% of Sz freq reduction in 19 pts (31%)
  - improvement of AEs in 16 pts (27%)

I. Era of Monotherapy

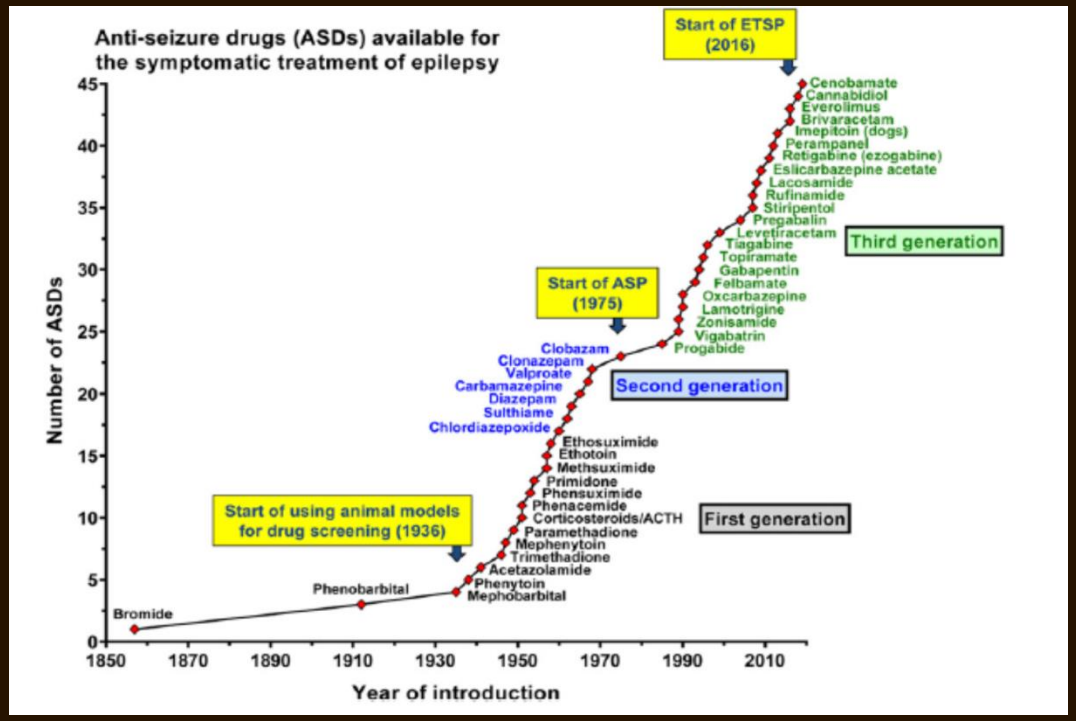
- **Monotherapy** provides similar efficacy as polytherapy but carries advantages of (Reynolds et al. Lancet 1976;1:923-926, Shorvon and Reynolds BMJ 1977;1:1635-1637, Shorvon and Reynolds BMJ 1979;2:1023-1025, Schmidt D J Neurol Neurosurg Psychiatry 1982 and 1983))
  - Less chance of immediate and delayed AEs.
  - Avoid drug interactions precipitating drug toxicities and/or Sz worsening.
  - Simpler regimen for accurate assessment of responses to individual drugs, better compliance and less costly

- Most patients do not require polytherapy -



II. New AED Era (1989- 2019)

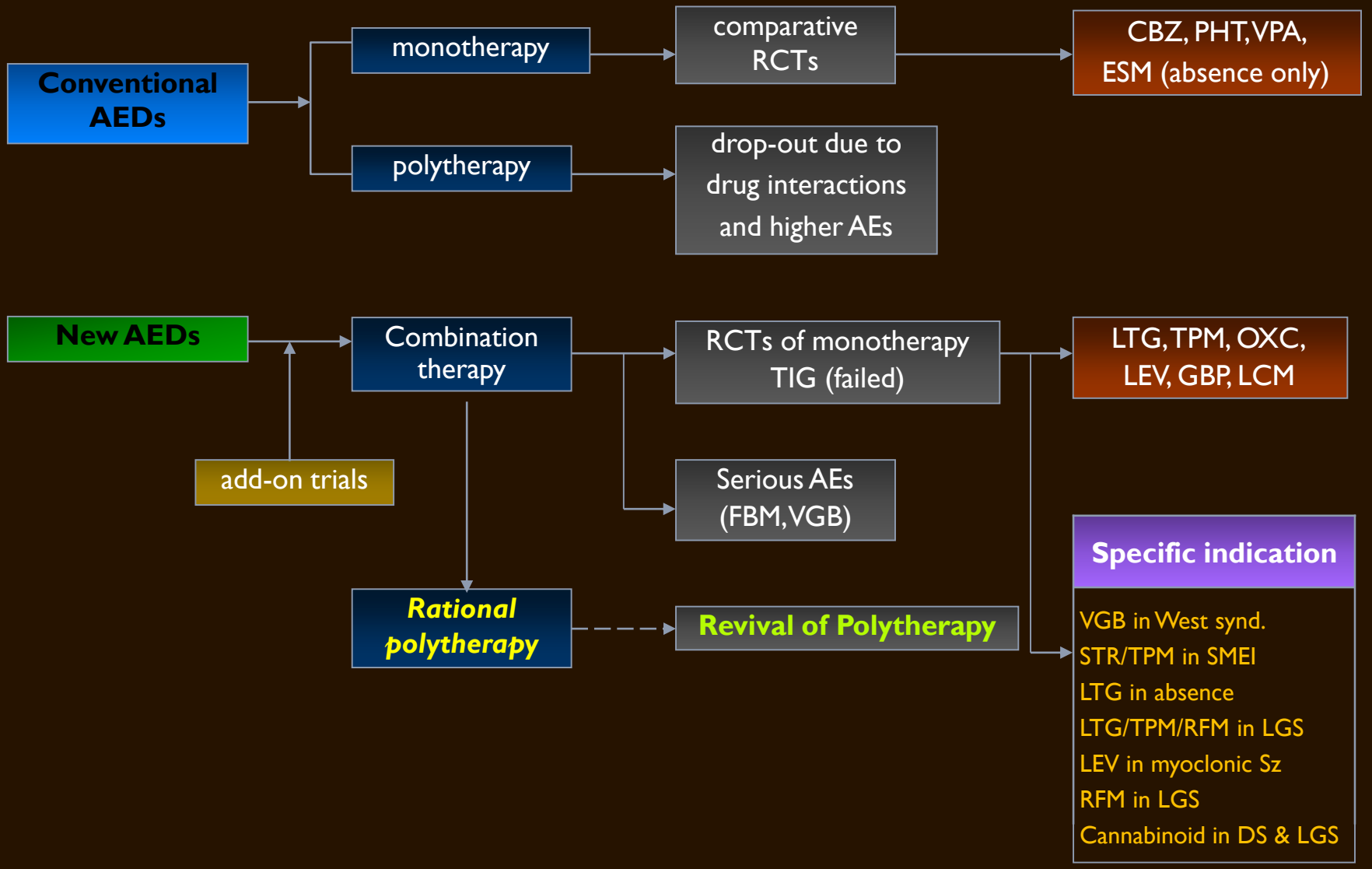
- **Introduced 19 new AEDs over past 3 decades: >25 AEDs available for Practice**
  - How to choose the best drug for given clinical scenarios ?



- **Clinical Trials: an essential step for Drug Development**
  - Double-blind, Placebo- controlled ,Adjunctive- therapy trial
    → primary tool to obtain regulatory approval of novel AEDs
    → All new AEDs were confirmed to be effective in add-on therapy (polytherapy)
  - Marketing approval : phase IV trials and PMS study
  - Monotherapy Trials (essential process for monotherapy indication)

II. New AEDs Era
I. Evidence-based Medicine

- **Clinical Development of AEDs: *New vs. Old***



II. New AEDs Era
- Impacts of New AEDs on AEDs Therapy -

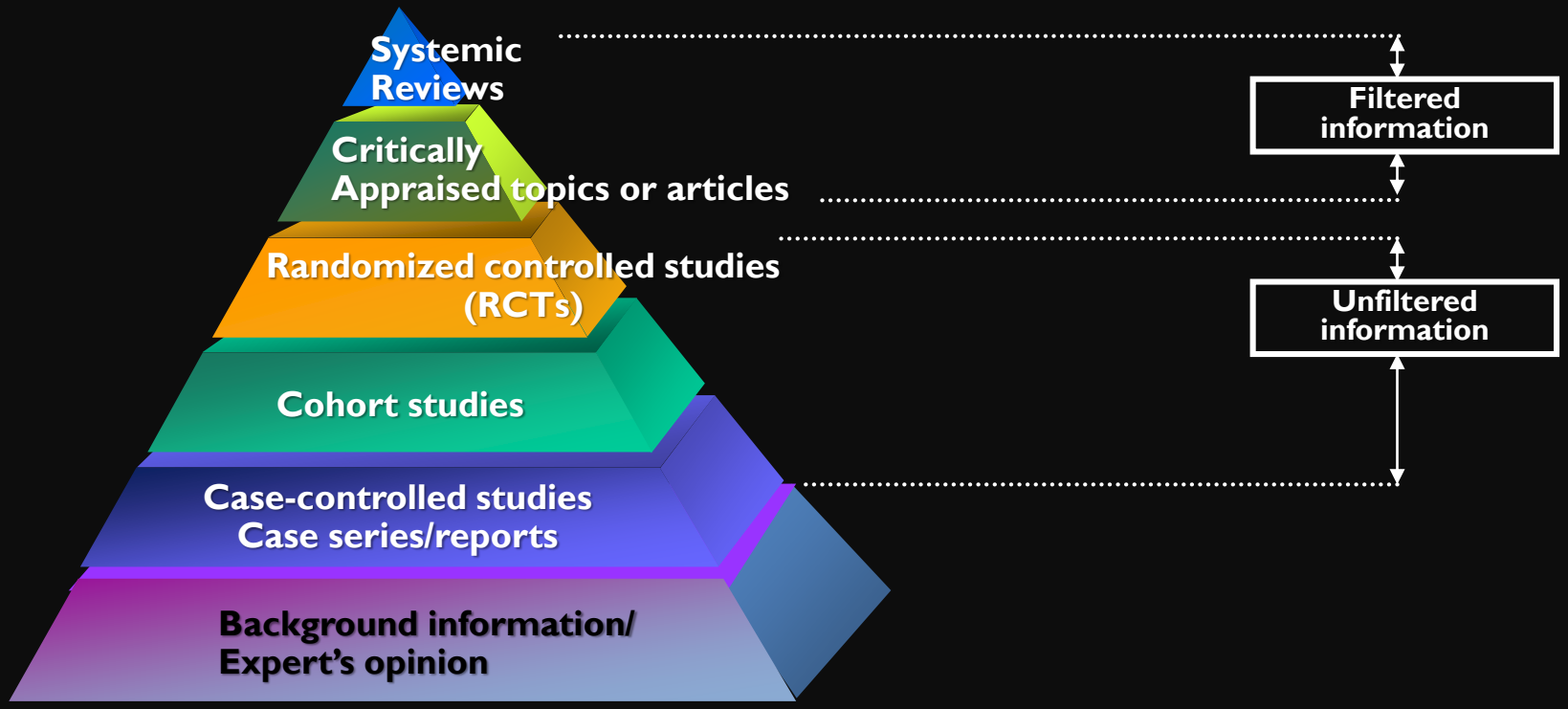
- Practice of Evidence- based Medicine (EBM)
- Paradigm Shift of Pharmacotherapy from "Disease-oriented" to "Patient-oriented" pharmacotherapy
- Revival of Polytherapy

II. New AEDs Era

1. Practice of Evidence-based Medicine

♣ Evidence Based Medicine (EBM)

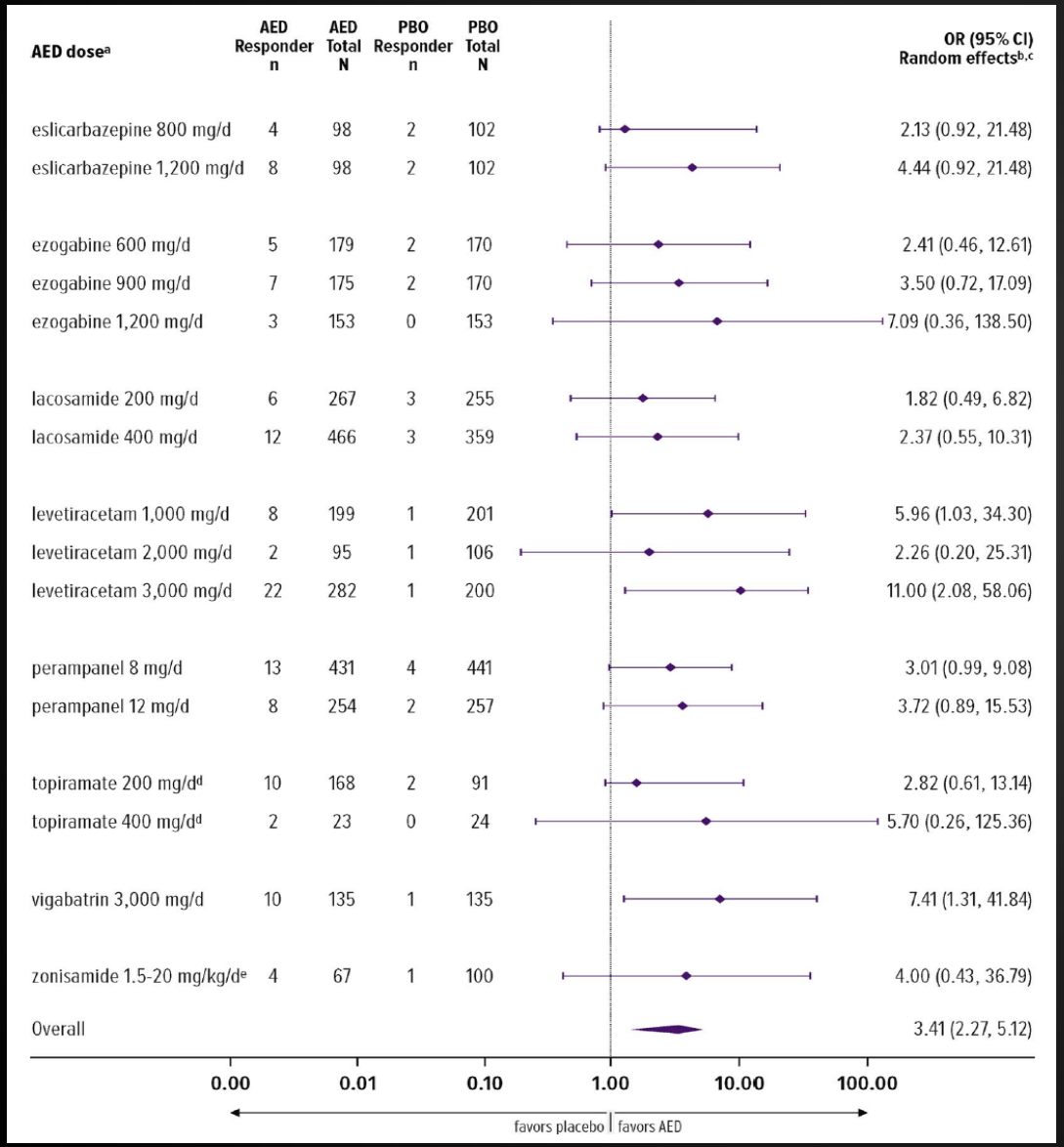
- Conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patient.
- Sources and hierarchy in the quality of Evidence



I. Evidence-based Medicine

Meta-analysis of Adjunctive Therapy of New AEDs

J Slatera et al. (Epilepsy Research 2018; 143: 120–129)



- N= 29 pivotal Trials Identifed 29 pivotal trials for 11 AEDs serving as the basis for US Food and Drug Administration (FDA) approval
- Patients treated with AEDs were more likely than placebo to achieve seizure response or freedom.
- Patients receiving pregabalin, tiagabine, and vigabatrin had the highest odds of ≥50% reduction in seizures
- patients receiving ezogabine, levetiracetam, and vigabatrin had the highest odds of seizure freedom.

Evidence-based AEDs Therapy
- Clinical Practice Guideline(CPG) -

- NICE-Guideline, 2012 (http://guidance.nice.org.uk)

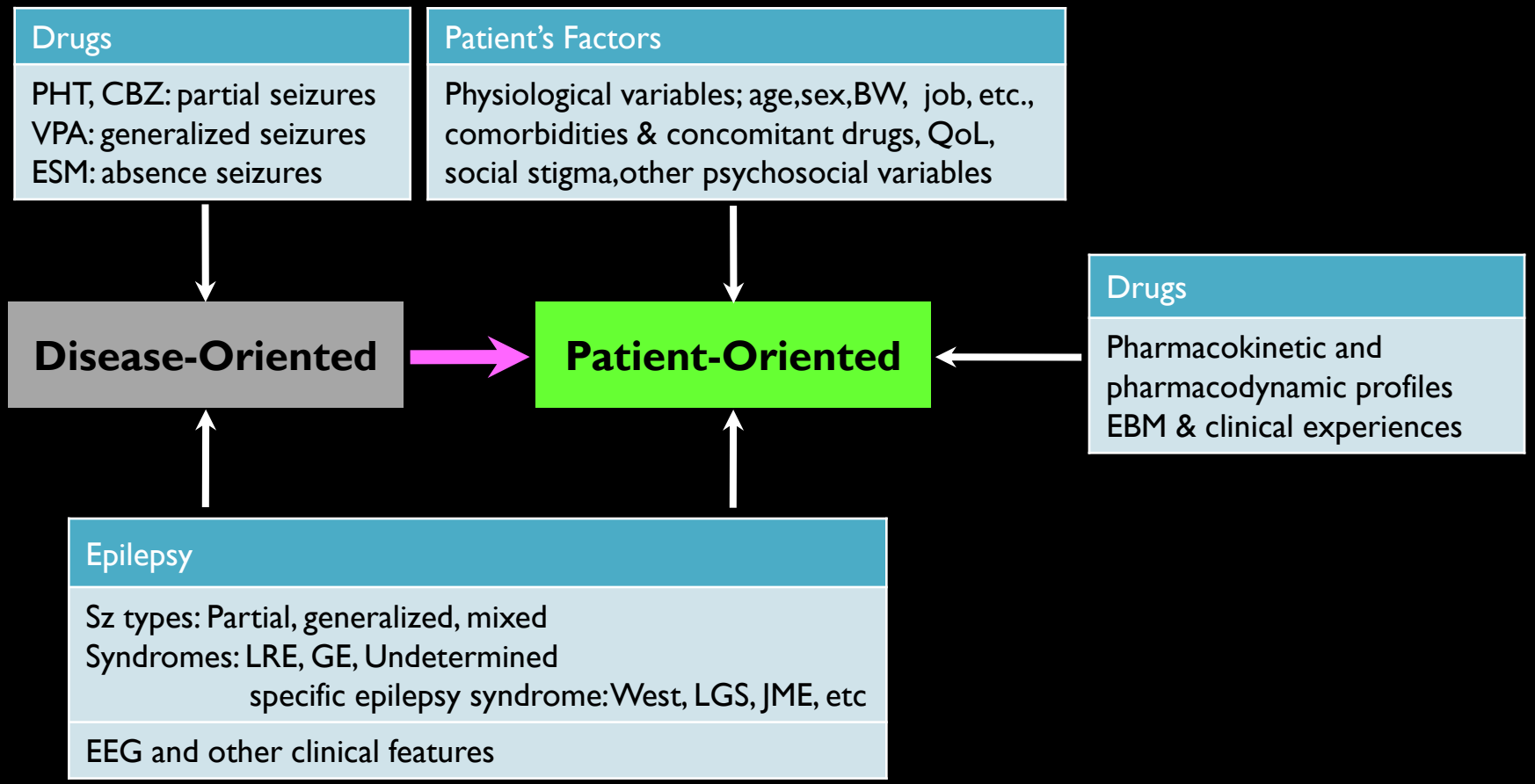
Seizure types	First-line AEDs	Adjuvant AEDs	Other AEDs at Tertiary Care center	Do not Offer AEDs
GTCs	CBZ, VPA, LTG, OXC	CLZ, VPA, LTG, LEV, TPM	-	(if three are absence Sz myoclonic Szs or if JME suspected) CBZ, GBP, OXC, PHT, PGB, TGB, VGB
Tonic or Atonic	VPA	LTG	RFM, TPM	
Absence	ESM, LTG, VPA	ESM, LTG, VPA	CLZ, CLB, LEV, TPM, ZNS	
Myoclonic	LEV, VPA, TPM	LEV, VPA, TPM	CLZ, CLB, ZNS, Piracetam	
Focal	CBZ, LTG, LEV, OXC, VPA	CBZ, CLB, GBP, LTG, LEV, OXC, VPA, TPM	ELC, LCM, PB, PHT, PGB, TGB, VGB, ZNS	
Prolonged or repeated Sz and convulsive SE in the community	Buccal MDZ Rectal DZ IV-LZ			

II. New Drug Era

2. Individual Patient-oriented AEDs Therapy

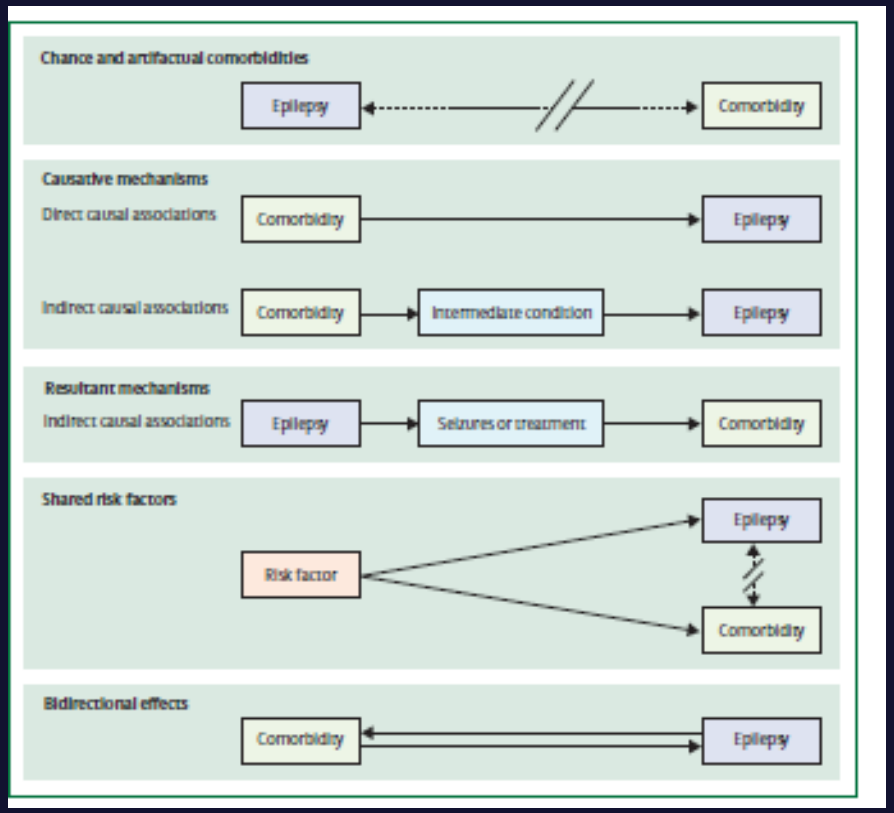
- **Epilepsy is beyond seizures:**

  AEDs Therapy should be focused at the patient's satisfaction and QOL



II. New Drug Era
2. Individual Patient-oriented Therapy
- Comorbidities -

- **Comorbidities:** *another disease occurring during the course of index disease*
  - *~50% of Patients with active epilepsy has at least one comorbid disease*
  - *Negative impact on QOL,*
  - *↑ use of health services and health cost,*
  - *↑ premature mortality*
  - *important factor for choice of AEDs*



Mechanisms of association between epilepsy and its comorbidities
(Keezer et al. Lancet Neurology 2016;15:106-115)

Keezer MR et al. Epilepsia 2015;56:e-68-85
Keezer MR et al. Lancet Neurol 2016;15:106-115
Forsgren L. Epilepsia 1992;33:450-456
Wolff JL et al. Arch Intern Med 2002;162:2296-76

Epilepsy beyond seizure: A Population-based Study of Comorbidities

Anbesaw W. Selassie et al. Epilepsy Research (2014) 108, 305—315

Table 3 Association of common comorbidities in persons with epilepsy and migraine compared to lower extremity fracture controls.

Comorbid condition	Epilepsy Adjusted[a]		Migraine Adjusted[a]	
	OR	(95% CI)	OR	(95% CI)
Somatic comorbidities				
Cardiovascular disease	1.97	(1.92—2.03)	1.45	(1.42—1.49)
Intestinal problems	1.54	(1.50—1.58)	1.59	(1.56—1.63)
Asthma/pulmonary	1.61	(1.57—1.65)	1.53	(1.50—1.56)
Gastric reflux	1.59	(1.55—1.63)	1.78	(1.74—1.81)
Anemia	1.91	(1.86—1.96)	1.18	(1.15—1.21)
Stroke	4.20	(4.06—4.34)	1.65	(1.59—1.71)
Diabetes	1.29	(1.26—1.33)	0.89	(0.86—0.91)
Peptic ulcer	1.57	(1.52—1.61)	1.78	(1.73—1.82)
Traumatic brain injury	1.59	(1.54—1.67)	0.81	(0.78—0.83)
Nutritional deficiency	2.27	(2.18—2.37)	0.83	(0.79—0.88)
GI bleed	1.80	(1.72—1.87)	1.42	(1.36—1.48)
Osteoporosis	0.87	(0.83—0.91)	0.65	(0.62—0.69)
Vision loss	2.47	(2.28—2.68)	1.33	(1.22—1.45)
Hearing loss	1.79	(1.67—1.93)	1.42	(1.31—1.53)
Parkinson's disease	2.45	(2.20—2.73)	1.01	(0.88—1.16)
HIV/AIDS	2.17	(1.91—2.45)	1.13	(0.98—1.29)
Multiple sclerosis	2.25	(1.98—2.54)	1.68	(1.50—1.89)
Migraine	3.37	(3.23—3.52)		—
Psychiatric and neurodevelopmental				
Depression	2.12	(2.06—2.17)	1.62	(1.59—1.66)
Anxiety	2.29	(2.23—2.35)	1.87	(1.82—1.91)
Psychoses	3.17	(3.06—3.28)	1.51	(1.46—1.56)
Schizophrenia	3.15	(2.94—3.37)	0.85	(0.78—0.92)
Personality disorder	3.61	(3.34—3.89)	1.67	(1.55—1.80)
Alcoholism	1.77	(1.71—1.82)	0.60	(0.58—0.62)
Drug abuse	2.37	(2.29—2.45)	1.19	(1.15—1.23)
Suicidal ideation/attempt	2.95	(2.81—3.10)	1.44	(1.38—1.52)
Alzheimer's dementia	2.19	(2.05—2.33)	0.61	(0.56—0.68)
Intellectual disability	12.88	(11.59—14.30)	0.48	(0.41—0.57)
Cognitive dysfunction	28.09	(23.33—33.82)	1.77	(1.38—2.26)
ADHD	2.31	(2.16—2.47)	1.56	(1.46—1.67)
Autism spectrum disorder	22.15	(16.77—29.26)	1.21	(0.81—1.80)

[a] Adjusted for age, race, gender, insurance status, and mortality status and number of comorbid conditions.

Choice of AEDs Related to Comorbidities in Epilepsy

Comorbidities	Choose	Avoid
Obesity ± DM	TPM, ZNS	GBP, PGB, VPA, PRP
Migraine	TPM, GBP, PGB, ZNS, VPA	
Skin rashes	LEV, GBP, PGB, TPM, VPA, PER, LAC	CBZ, LTG, OXC, PHT, PB
Neuropathic pain	PGB, GBP, CBZ, OXC, PHT, LTG	
Depression± behavioral dis	LTG, CBZ, OXC, VPA, PGB	LEV, PB, TPM, ZNS, PER
Cognitive dysfunction	LTG, LEV, OXC, LAC	PB, TPM, ZNS
Concomitant drugs	GBP, LEV, PGB, LAC, ZNS	Enzyme- inducers or inhibitors
Cancer	LEV, VPA, PER	Enzyme- inducers
Cardiac arrhythmia		Sodium channel blockers
Glaucoma		TPM
Gait disturbances		CBZ. PHT, PER
Heat stroke		TPM, ZNS
Hematological disorder		CBZ, VPA
Hyponatremia		OXC, ESL, CBZ
Hepatic disease	Drugs excreted by renal excretion	VPA, CBZ, PB, OXC
Renal disease	Drugs excreted by hepatic metabolism	GBP, PGB, LEV
Hyponatremia		OXC, ESL, CBZ
Osteoporosis	LTG, LEV	Enzyme inducers, TPM, VPA, ZNS
Restless leg syndrome	GBP, PGB, CZP	
Parkinson dis	ZNS	
Tremor	TPM, PB, PRM	

CBZ; carbamazepine, CZP; clonazepam, GBP: gabapentine, LAC; lacosamide LEV: levetiracetam, LTG; lamotrigine, OXC; oxcarbazepine, PB; phenobarbital, PRM; primidone, PER: perampanel, PGB; pregabalin, TPM; topiramate, VGB; vigabatrin, VPA; valproic acid, ZNS; zonisamide, EI-drug: enzyme-inducing drugs, SCB; sodium-channel blockers

II. New AEDs Era
3. Revival of Polytherapy

- **"A large pool of AEDs"** carrying diverse pharmacological profiles
  - Diverse mechanisms of action
  - Better pharmacokinetic profiles and less drug interactions
  - Better safety and tolerability
  - Efficacy proven by RCTs as Add-on Therapy

→ ***All New AEDs were used in Polytherapy at the beginning***

↑ Controversies about Monotherapy vs. Polytherapy

♣ Case Scenario *(Stephen et al, Lancet 1998)*

- 18 y.o M with 1 to 2 Szs (CPS ± 2GTCS)/week under PHT-monotherapy
  - trial of several AEDs & Lt ATL
  - referred to the Epilepsy Clinic in 1992
    - add-on Vigabatrin – no help to D/C
    - add-on LTG: minimal Sz reduction
      → change to LTG monotherapy 800mg/day (D/C PHT)
    - add-on TPM: 75mg/day → Sz Free Since

- Why "Sz Free" after TPM add-on?
  - *due to effects of TPM alone?*
  - *due to phamacodynamic interaction of LTG and TPM?*
  - *due to a part of natural course?*

3. Revival of Polytherapy
- Controversies on Monotherapy vs. Polytherapy -

- **Monotherapy Preferred to Polytherapy, Why ?**
  - Compliance is poorer than monotherapy --------- *really?*
  - ↑ Risk of drug interactions --------- *really?*
  - ↑ Side effects --------- *really?*
  - Efficacy is same --------- *really?*

3. Revival of Polytherapy
- Controversies on Monotherapy vs. Polytherapy -

(1) Is Compliance poorer in Polytherapy than Monotherapy ?

- Coleman CI, et al. (J Manag Care Pharma. 2012;18:527–539)
  - *Meta-analysis of 51 publications with electronic adherence monitoring in multiple diseases*

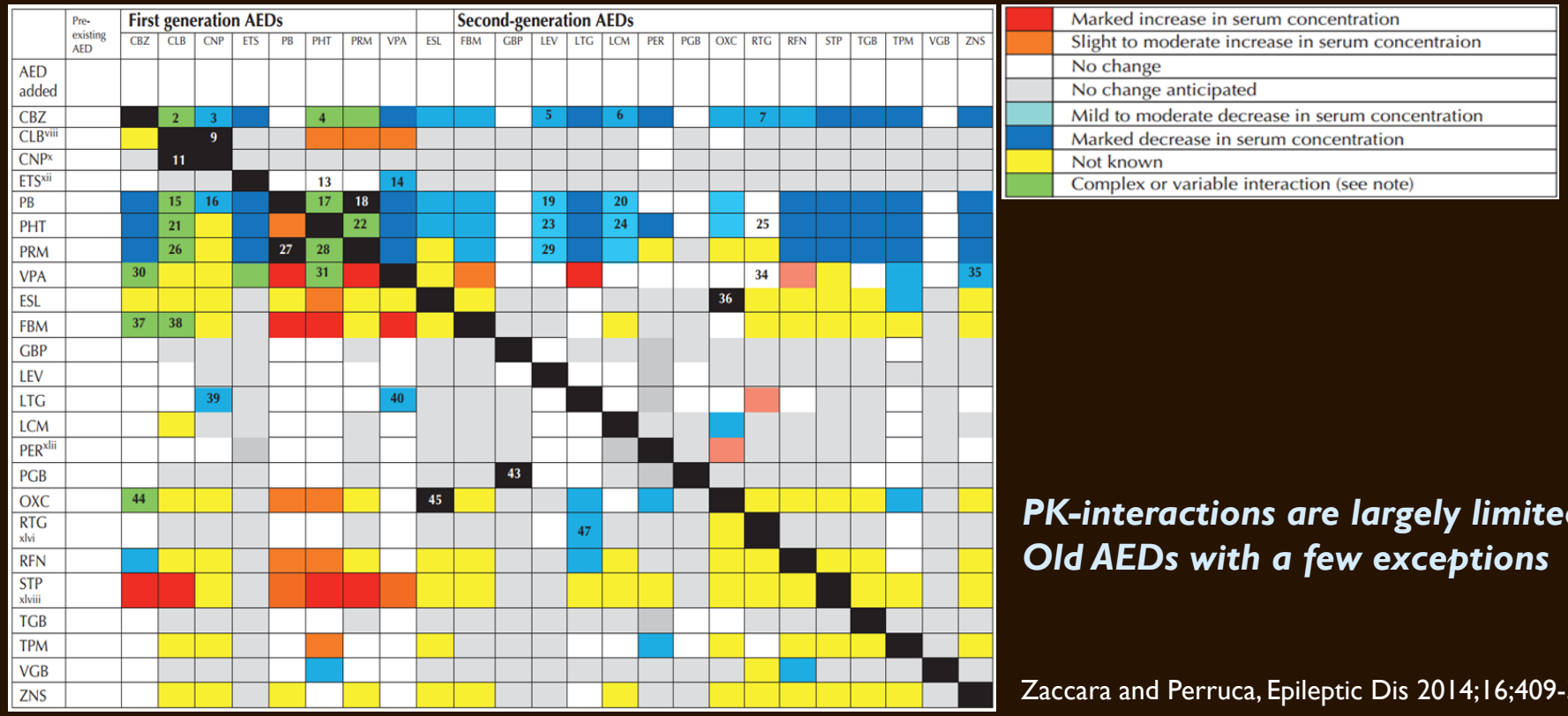
Timing Adherence (Percentage of doses taken within assigned intervals)	
	Improvement with QD dosing
QD vs. BID	**+26.7%**
QD vs. TID	**+39.0%**
QD vs. QID	**+54.2%**

  - ***Dosing frequency*** *is the single most important factor affecting medication adherence*
  - *Studies on the compliance between monotherapy vs. polytherapy revealed conflicting results*

Controversies on Monotherapy vs. Polytherapy

(2) Risks of Drug Interaction: Higher in Polytherapy than Monotherapy ?

- **Pharmacokinetic Interactions:**
  - Common, usually due to 'enzyme induction or inhibition' ☞ mostly predictable
  - Plasma protein binding interactions are usually of little clinical significance
  - Managed by dosage adjustments being guided by clinical observation and drug level monitoring
  - They do not improve the therapeutic index (ED50/TD50) of the individual drugs



PK-interactions are largely limited to Old AEDs with a few exceptions

Zaccara and Perruca, Epileptic Dis 2014;16;409-32

Controversies on Monotherapy vs. Polytherapy

(2) Risks of Drug Interactions: *Higher in Polytherapy than Monotherapy ?*

- **Pharmacodynamic Interactions**
  - Related to interactions involving **Mechanisms of Action(MOA)**
  - Additive, Supra-additive and Infra-additive in either therapeutic or adverse effect profiles
  - The therapeutic index($TI = TD_{50}/ED_{50}$) of combination regimen may be changed from the TI of the individual drugs
  - ***Difficult to Assess***
    - Animal experiments are time consuming, and their extrapolation to the clinic unclear
    - Preclinical assessment: Isobolographic analysis
      Protective index measurement in specific Sz model
    - In Clinical Trials, no ideal trial designs yet applied:
      - Sequential trials of monotherapy followed by combination therapy (Pisani et al. 1999) may be the best alternative

Asessment of Pharmacodynamic Interactions

(1) Experimental Models:

- Comparison of TI of individual AEDs between monotherapy and combination therapy in specific animal models

Table 1. Effects of anticonvulsants administered alone and in combination with LEV in the mouse audiogenic seizure model

Name of the compound	Pretreatment time[a] (min)	ED_{50A} (mg/kg)[b] VEH plus Compound	ED_{50B} (mg/kg)[c] LEV[d] plus Compound	Change in potency ED_{50A}/ED_{50B}
Valproate	30	121 (110–144)	4.3 (1.8–9.7)	28[e]
Clonazepam	30	0.036 (0.033–0.039)	0.0016 (0.0007–0.0031)	23[e]
Diazepam	30	0.33 (0.31–0.35)	0.017 (0.0004–0.8)	19[f]
NBQX	15	27.9 (18.6–41.7)	1.5 (0.68–3.31)	19[f]
MK-801	30	0.17 (0.15–0.2)	0.01 (0.0004–0.28)	17[f]
Phenobarbital	30	9.6 (6.8–12.1)	0.6 (0.2–1.3)	16[e]
Chlordiazepoxide	30	2.9 (2.2–3.8)	0.18 (0.11–0.31)	16[f]
Bretazenil	30	0.19 (0.17–0.21)	0.017 (0.008–0.012)	11[f]
NO-711	30	2.5 (2.1–3.1)	0.5 (0.22–1.22)	5[f]
Lamotrigine	30	16.8 (14.3–19.7)	4.1 (2.0–8.7)	4.1[f]
Allopregnanolone	10	6.3 (5.8–6.9)	1.7 (0.9–5.5)	3.7[f]
Carbamazepine	30	21.2 (13.3–28.4)	5.9 (3.9–8.1)	3.6[e]
Vigabatrin	240	1367 (1331–1404)	490 (409–587)	2.8[f]
Phenytoin	30	25.7 (19.6–32.8)	13.2 (9.3–16.5)	1.9[e]
Propranolol	30	19.9 (18.5–21.5)	11.6 (9.8–13.6)	1.7[f]
Flunarizine	60	132 (118–147)	77.5 (48.1–124.7)	1.7[f]

Audiogenic seizures were induced in genetically sound susceptible mice (Animal Husbandry Unit, UCB, Belgium) with 90-dB, 10- to 20-kHz acoustic stimulus applied for 30 s. Each experimental group consisted of 10 mice that responded positively in the preselection testing performed 24 h before the experiment.
[a]All compounds were administered i.p.
[b]ED50A, dose of an anticonvulsant that was required to protect 50% animals against clonic seizures induced by audiogenic stimulation; 95% confidence intervals in parenthesis.
[c]ED50B, dose of an anticonvulsant in combination with levetiracetam that was required to protect 50% animals against clonic seizures induced by audiogenic stimulation; 95% confidence intervals in parenthesis.
[d]Levetiracetam (LEV) was administered at the dose of 5.5 mg/kg i.p. 60 min prior to testing.
[e]Reported only in the abstract form (Matagne et al., 2001).
[f]Previously unpublished.

Kaminski et al., Epilepsia 2009;50:387-397

Assessment of Pharmacodynamic Interaction

(1) Experimental Models

- Isobolographic Analysis

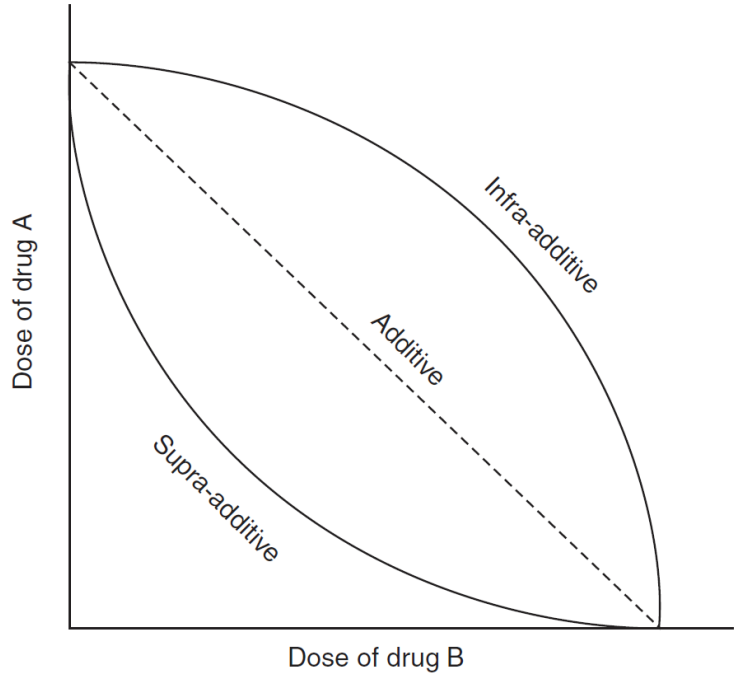


Fig. 1. Hypothetical isobologram showing the doses of two drugs required to produce a specified effect (either efficacy or toxicity) where the drugs have additive, supra-additive (synergistic), or infra-additive (antagonistic) effects.

Table I. Theoretical interactions between two drugs[a,b]

Efficacy	Toxicity
Infra-additive	Infra-additive
Infra-additive	Additive
Infra-additive	Supra-additive
Additive	Infra-additive
Additive	Additive
Additive	Supra-additive
Supra-additive	Infra-additive
Supra-additive	Additive
Supra-additive	Supra-additive

a Pure 'additive' implies absence of a positive interaction.

b The ideal interaction would be supra-additive for efficacy but infra-additive for toxicity.

Kaminski et al., Epilepsia 2009;50:387-397

Effects of AED Combinations Evaluated with Isobolography in Mice

(Lason et al. – Phamacological Reports,2011;63:271-292)

Drug A	Drug B					
	LTG	OXC	TGB	TPM	VGB	VPA
CBZ	Ant^{Add}	Add^{Add}	Add^{NE}	S^{NE}	NE	NE
GBP	S*	S^{0}	S^{Add}	S^{Add}	S^{0}	S^{Add}
LEV	Add^{0}	S^{0}	NE	S^{0}	NE	Add^{0}
OXC	Ant^{Syn}	-	Add^{Add}	S^{Add}	NE	Add^{Add}
TGB	Add^{Ne}	Add^{An}	-	Add^{NE}	S^{Add}	Add^{Ne}
TPM	S^{An}	S^{Add}	Add^{Ne}	-	NE	NE
VPA	S^{An}	Add^{Add}	S^{Ne}	NE	Add^{0}	-

Ant – Antagonism; S – synergy; Add – additivity; * – the increased level of GBP in brain has been observed; o– no neurotoxicity observed for antiepileptics at the fixed dose ratio of 1:1, recorded in the chimney test or passive avoidance task; Add– additive neurotoxicity in the chimney test calculated by isobolography; An – antagonistic neurotoxicity; Syn– synergistic neurotoxicity; CBZ – carbamazepine; GBP – gabapentin; LEV –levetiracetam; LTG – lamotrigine; – – no possibility of combination; – neurotoxicity not evaluated; NE – not evaluated by isobolography; OXC– oxcarbazepine; – synergistic neurotoxic effects; TGB – tiagabine; TPM – topiramate; VGB – vigabatrin; VPA – valproate

Effects of AED Combinations Evaluated with Isobolography

Triple Combination Therapy

- **JJ Luszczki et al.** (Pharmacological Reports: https://doi.org/10.1007/s43440-020-00117-y)
  - Isobolographic analysis of seizure activity in mice was evoked by alternating current stimulation (25 mA, 500 V, 50 Hz, 0.2 s) in a fixed ratio combination of 1:1:1.
  - The interaction of LCM add-on to LTG+VPA combination was sub-additive with isobolography

Table 1. Interactions for the studied three-drug combinations of AEDs in the MES –induce seizure test in mice

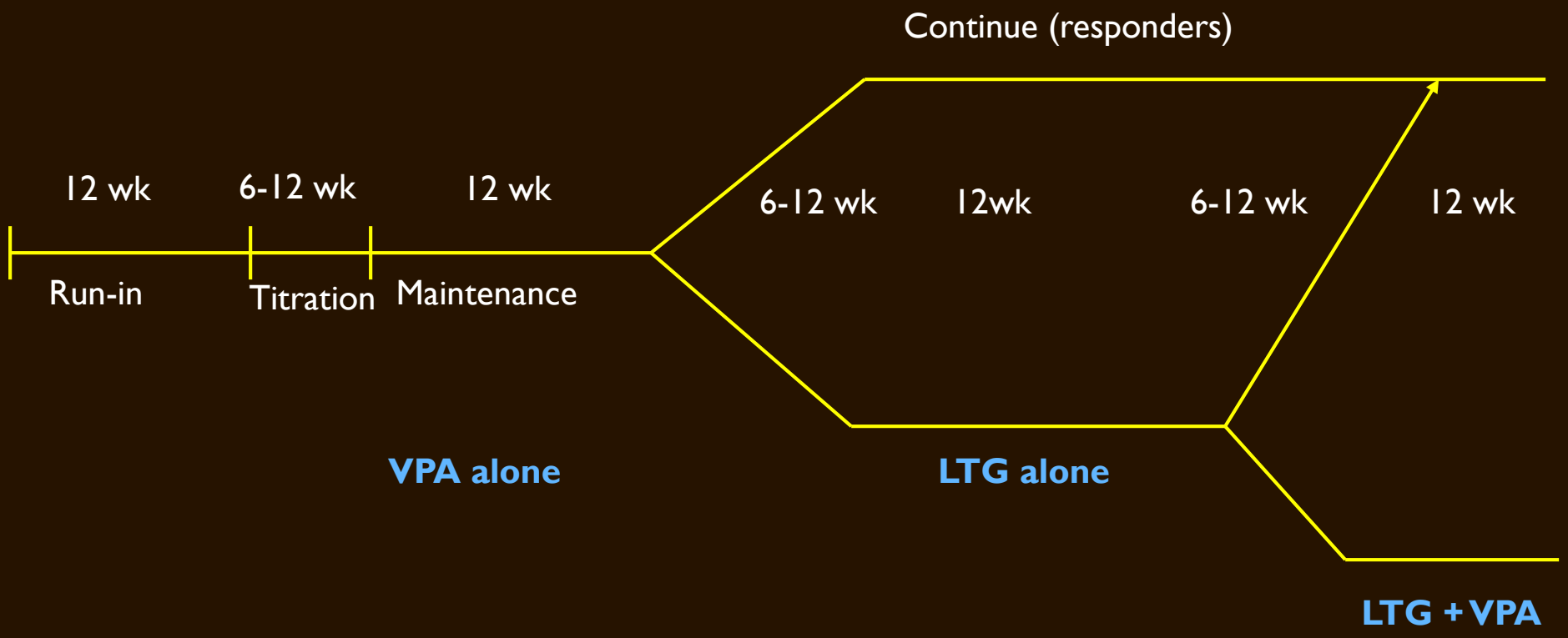
Combination of three antiepileptic drugs	Type of interaction	References
Lacosamide + lamotrigine + valproate	Infra-additive	(This study)
Lacosamide + carbamazepine + valproate	Infra-additive	[37]
Lacosamide + carbamazepine + lamotrigine	Additive	[36]
Lacosamide + carbamazepine + phenobarbital	Additive	[31]
Lacosamide + lamotrigine + phenobarbital	Additive	[35]
Carbamazepine + phenobarbital + valproate	Additive	[39]
Carbamazepine + phenobarbital + topiramate	Supra-additive	[41]
Oxcarbazepine + pregabalin + topiramate	Supra-additive	[38]
Phenobarbital + phenytoin + pregabalin	Supra-additive	[43]

- Combining two Na-channel blockers seems infra-additive

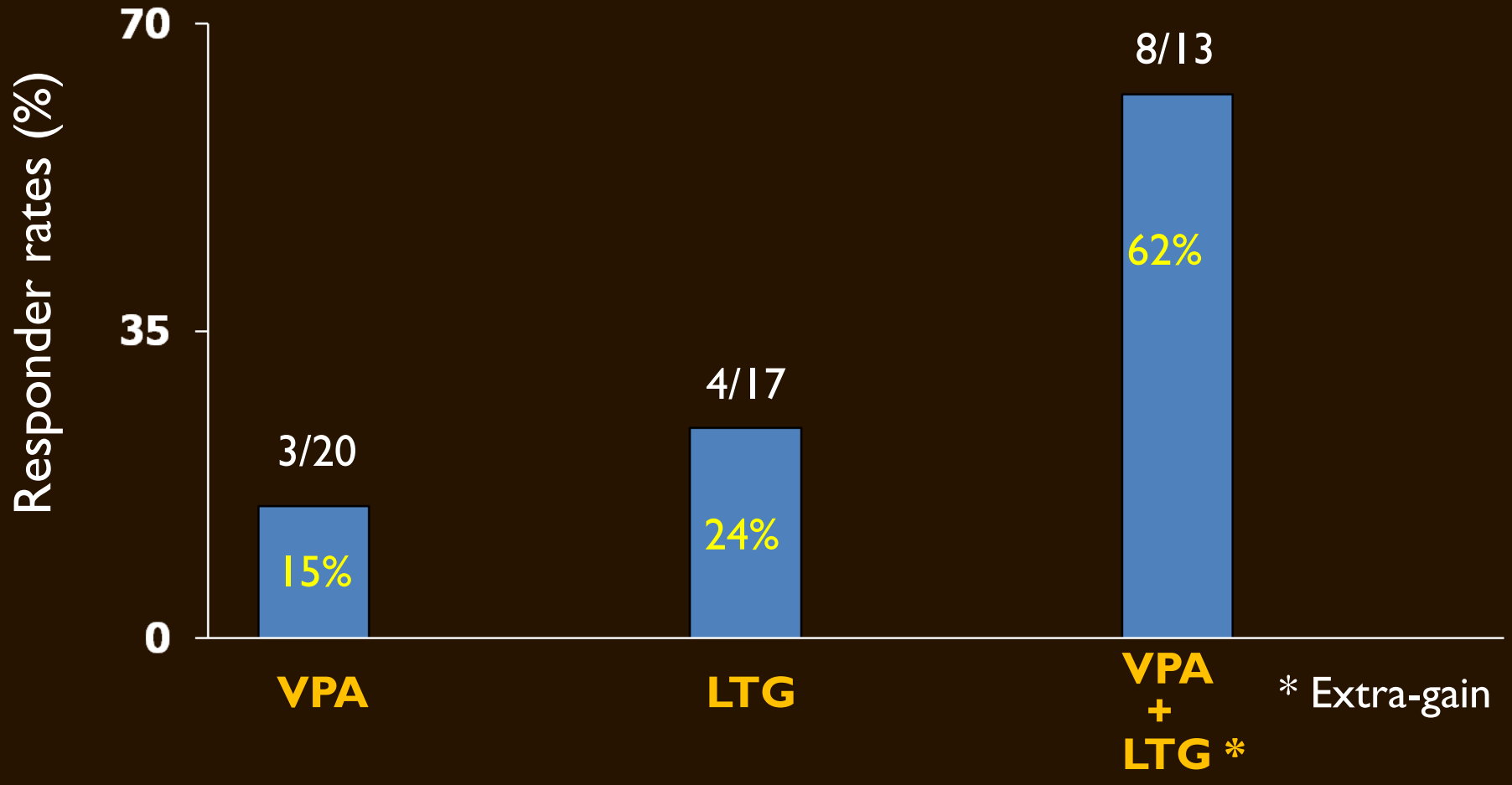
Assessment of Pharmacodynamic Interactions

(2) Clinical Studies

- **Pisani et al.,** (Epilepsia 1999; 40:1141-6)
  - ***Sequential Trial of Valproate, Lamotrigine and their Combination in Partial Epilepsy***



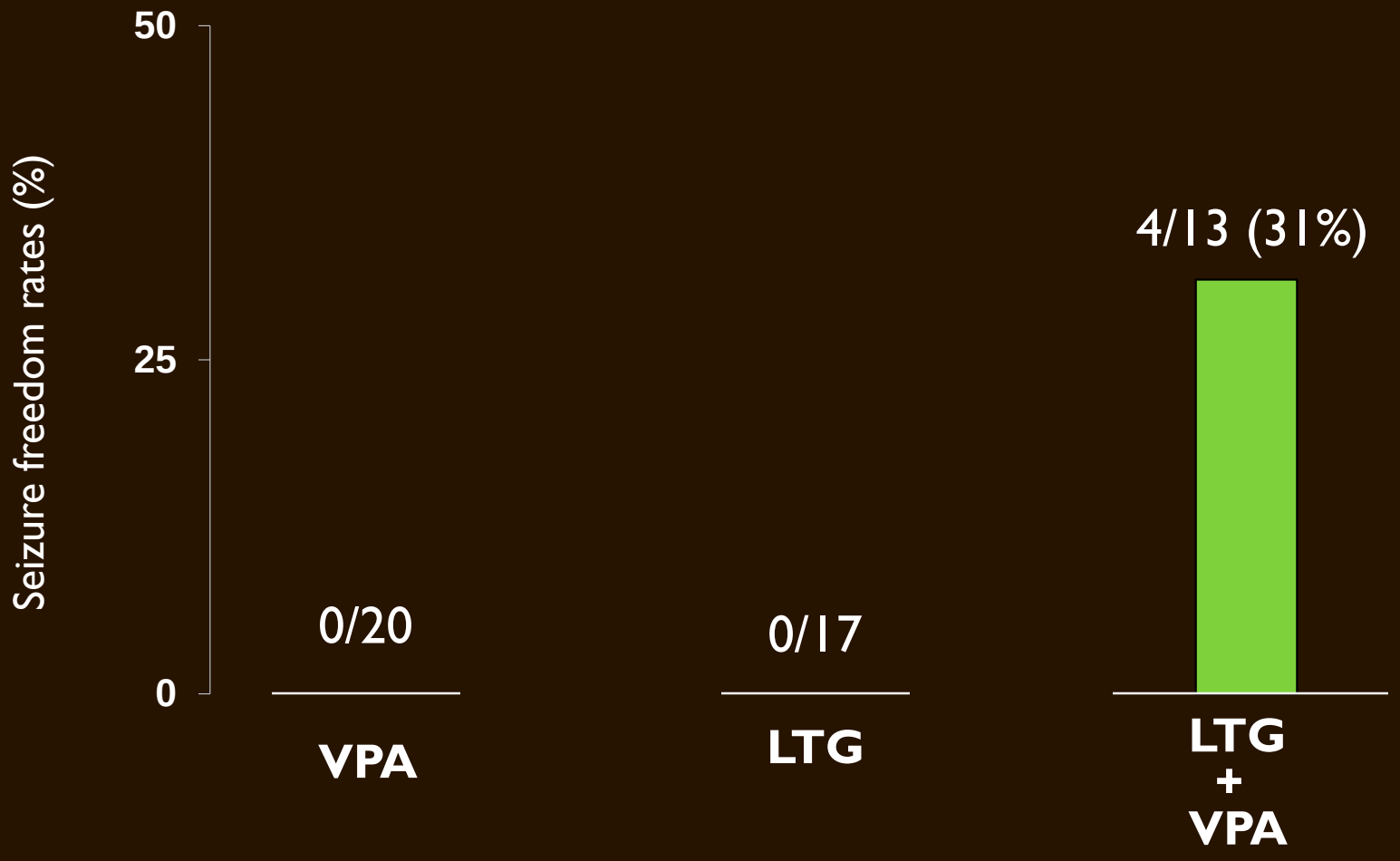
Valproate, Lamotrigine and their Combination:
50% Responder Rates



Disclaimer: valproate-lamotrigine co-administration enhances risk of serious cutaneous reaction

Pisani et al, Epilepsia 1999; 40: 1141-6

Valproate, Lamotrigine and their Combination:
Seizure Freedom Rates



Disclaimer: valproate-lamotrigine co-administration enhances risk of serious cutaneous reaction

Pisani et al, Epilepsia 1999; 40: 1141-6

Combination Regimens Carrying Synergistic Interactions

Combination Regimen	Level of Evidence	References
LTG and VPA	+++	Brodie and Yuen(1997), Pisani et al.(1999)
ESM and VPA (absence seizure)	++	Rowan et al. (1983)
LTG and TPM	+	Stephaen et al.(2010)
LCM and LEV	++	Chung et al. (2010)
LTG and LEV	++	Kinirons et al.(2006), Legge et al.(2018)
OXC and LEV	+	Legge et al.(2018)
CBZ and VPA	+	Stephen et al. (2012)
VPA and CLB and STR (Dravet syndrome)	+++	Chiron et al. (2000)
LTG and VPA and BDZ (epileptic encephalopathy)	++	Machado et al. (2011)
VGB and Hormones (Infantile Spasm)	+++	O'Callaghan et al.(2017)

+++; controlled trials, ++; case series studies, +; anecdotal

BDZ; benzodiazepines, CBZ; carbamazepine, ESM; ethosuximide, CLB; clobazam, LCM; lacosamide, LEV; levetiracetam, LTG; lamotrigine, OXC; oxcarbazepine, STR; stiripentol, VGB; vigabatrin, VPA; valproate

Pharmacological Profile of the Novel Antiepileptic Drug Candidate Padsevonil: Characterization in Rodent Seizure and Epilepsy Models

Karine Leclercq, et al. J Pharmacol Exp Ther 372:11–20,

Padsevonil, (4R)-4-(2-chloro-2,2-difluoroethyl)- 1-{[2-(methoxymethyl)-6-(trifluoromethyl)imidazo[2,1-b] [1,3,4] thiadiazol-5-yl]methyl}pyrrolidin-2-one (padsevonil), is an antiepileptic drug (AED) candidate: rationally designed compounds with high affinity for synaptic vesicle 2 (SV2) proteins and low-to-moderate affinity for the benzodiazepine binding site on GABAA receptors.

Padsevonil has much higher T.I. than either BRV, LEV, BDZ or other AEDs

Comparison of the therapeutic index of padsevonil and nine other antiepileptic drugs with different mechanisms of action determined in the mouse amygdala kindling model and rotarod test.

Other than padsevonil, brivaracetam, and valproate, the ED_{50} values—and, therefore, the therapeutic index of the other antiepileptic drugs—could not be calculated.

Drug	Amygdala Kindling ED_{50}	MAD/Protection Against Seizures[a]	MTD/Protection Against Seizures[a]	Rotarod Test TD_{50}	Therapeutic Index
	mg/kg	*(mg/kg)/%*	*(mg/kg)/%*	*mg/kg*	
Padsevonil	1.2 (0.4–3.4)	1.4/60	13.9/100	12 (9–15)	9.8
Brivaracetam	68 (39–118)	134/90	212/91	195 (133–245)	2.8
Levetiracetam	—	540/60	540/60	1389 (962–2041)	—
Valproate	239 (169–338)	250/56	400/89	298 (201–418)	1.2
Phenytoin	—	>70/0	70/0	129 (76–194)	—
Carbamazepine	—	56/89	56/89	36 (27–48)	—
Lamotrigine	—	>56/33	56/33	20 (13–27)	—
Diazepam	—	3/89	3/89	3 (2–4)	—
Topiramate	—	>300/25	300/25	249 (150–357)	—
Retigabine	—	15/100	15/100	12 (8–18)	—

MAD, minimally active dose, defined as the lowest dose providing statistically significant protection against focal to bilateral tonic-clonic seizures; MTD, maximal tested dose, defined as the highest dose tested in the amygdala kindling model;—, not calculated.

[a]Protection against focal to bilateral tonic-clonic seizures.

Controversies on Monotherapy vs. Polytherapy

(3) Does Polytherapy cause more Side Effects ?

- **an observation study for epilepsy after first drug failure** (Kwan and Brodie., 2000)

	Sz free	intolerable AEs	
2nd mono (n=35)	17%	26%	
duotherapy (n=42)	26%	12%	P=0.25

- **open-randomized uncontrolled trial** (Beghi et al., 2003)

	Sz free	retention rate	AEs
monotherapy (n=76)	14%	55%	51%
duotherapy (n=81)	16%(P=0.74)	65%(P=0.74)	34%(P=0.07)

Concept of Total Drug Load
(Lammers at al. Epilepsia 1995:36:440-446)

- Total Drug Load (TDL): Ratio of prescribed daily dose(PDD) to defined daily dose (DDD) by WHO-guideline

- Measured AEs by Neurotoxicity index and Systemic toxicity index to correlate with stratified TDL in clinic patients
  - TDL≤2/day: Monotherapy(n=169) vs. Polytherapy(n=120)
    no differences in AE-index
  - TDL>2/day: none in monotherapy were able to tolerate
    134 pts in Polytherapy: AEs in 70%~100%
    if TDL≥4/day: All pts represented AEs

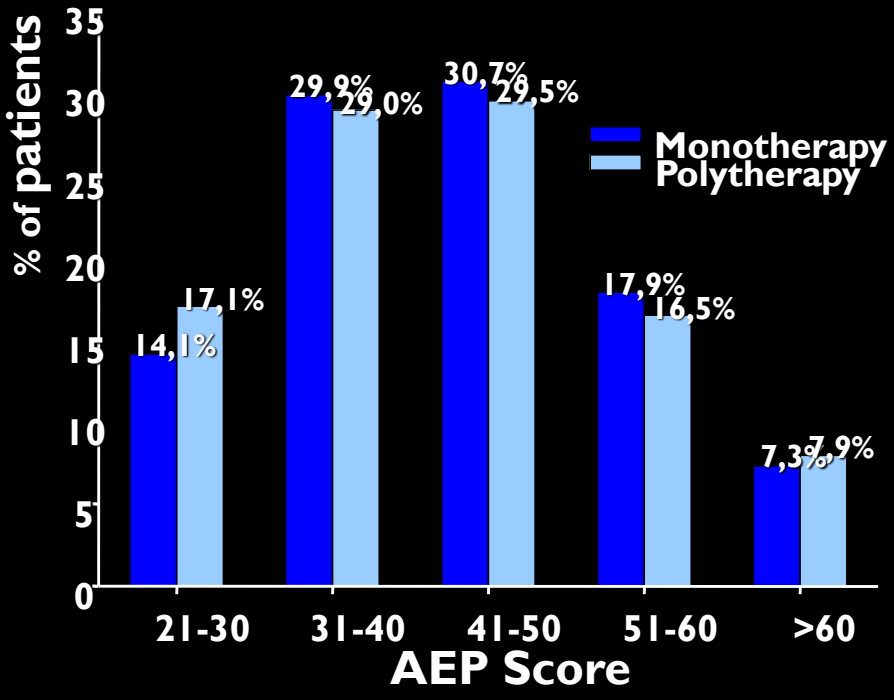
- **Conclusion:**
  - Higher incidence of AE in patients under polytherapy is related to higher TDL
    - if TDL is kept < 2.0/day, AEs are comparable
  - Patients under monotherapy cannot tolerate TDL>2.0/day, whereas patients under polytherapy may better tolerate higher TDL

Does Polytherapy Cause More Side Effects ?

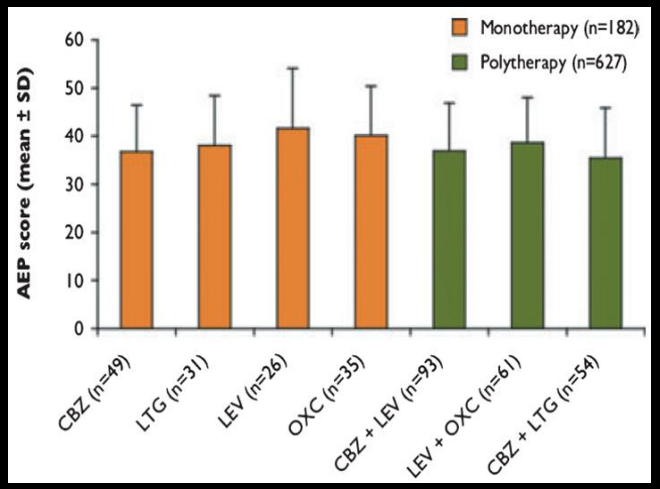
Canevini MP et al. (Epilepsia 2010;51:797-804)

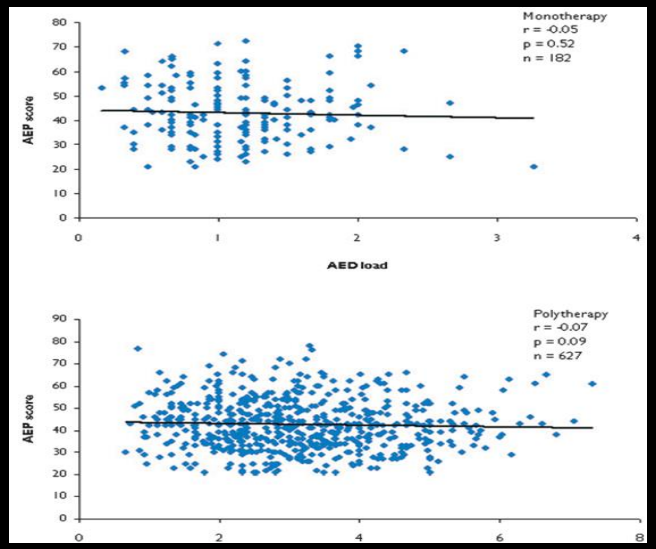
- AEs were not related to any specific AEDs, the number of AEDs, total drug loads, age, Sz frequency, etc.
- AEs were related to female gender and depressed mood.

❖ **Burden of AEs in adult pts with DRE (N=790)**



Monotherapy vs. Polytherapy is not an issue for the Tolerability or Safety





Controversies on Monotherapy vs. Polytherapy

(4) Is Efficacy of Polytherapy same as Monotherapy?

- Two representative studies were numerically in favor of combination therapy than monotherapy but failed to convincing evidence

- **an observation study for epilepsy after first drug failure** (Kwan and Brodie., 2000)

	Sz free	intolerable AEs	
2nd mono (n=35)	17%	26%	
duotherapy (n=42)	26%	12%	P=0.25

- **open-randomized uncontrolled trial** (Beghi et al., 2003)

	Sz free	retention rate	AEs
monotherapy (n=76)	14%	55%	51%
duotherapy (n=81)	16%(P=0.74)	65%(P=0.74)	34%(P=0.07)

Longitudinal Outcomes of AEDs Therapy

- ***Glasgow Hospital Cohort Studies*** (Kwan and Brodie N Engl J Med 2000; 342: 314-9, Mohanraj R, Brodie MJ. Eur J Neurol 2006; 13: 277-82, Brodie MJ et al. Neurology 2012;78:2548-1554, Chen et al. JAMA Neurol 2018;75: 279-286)
  - In patients who failed to first two drug regimen, Seizure free rate was 1 % in response to 3rd drug monotherapy and 3 % during combination therapy in 2000
  - In cumulative longitudinal cohort studies, SFR by monotherapy was unchanged but SFR by combination therapy increased from 3% to 8.4%(~ 3 fold increase)

Recruitment	N	One AED	Multiple AED	Total
1982-1997	470	61	3.0	64.0
1982-2001	780	59	5.4	64.4
1982-2005	1098	61.9	6.4	68.3
1982-2012	1795	55.3	8.4	63.7

- ***Outcome of AEDs therapy was improved only in patients undergoing polytherapy !***
- ***Lack of superiority of New AEDs compared to Old AEDs in Monotherapy Trials predicted no significant improvement of outcomes in Monotherapy***

II. New AEDs Era: 3. Revival of Polytherapy

- Controversies on Monotherapy vs. Polytherapy -

(4) Is Efficacy of Polytherapy same as Monotherapy?

- No Class-I evidence for any differences between Monotherapy vs. Polytherapy

- A fair comparison between Monotherapy and Polytherapy requires
  - Balanced baseline patient characteristics
  - Appropriate dose-titration schedules including initial target dose
  - Equivalent Total Drug Load
  - **Appropriate Combination Regimen** (having synergistic interactions) to compare with Monotherapy regimen

  → These Trials are difficult to conduct in patients with refractory seizures, but feasible in patients with newly diagnosed epilepsy as the first drug regimen

Is Efficacy of Polytherapy same as Monotherapy ?
- Monotherapy Trials in Newly Diagnosed Epilepsy -

- **DBRCTs in Patients with Newly Diagnosed Epilepsy**

  (Deckers CLP et al.Epilepsia 2001;42:1187-1394)

  - N=130, CBZ 400mg vs CBZ 200mg + VPA 300mg (TDL=0.4) FU:12month
  - RESULTs
    - **Completion rate:** 61% in Mono vs 70% in Poly (p=0.16)
    - **Withdrawal due to AEs:** 22% in Mono vs 14% in Poly (p=0.15)
    - **Seizure Free** at 12 mo: 86% in Mono vs 74% in Poly
    - No differences in QOL
- **Conclusion:**
  - No differences between "CBZ" and "CBZ+VPA" at equivalent TLD (PDD/DDD)
  - A trend for better tolerability of "CBZ+VPA"
- **Criticism:**
  - *CBZ+VPA has significant pharmacokinetic interactions and lacks synergistic interactions in clinical practice – not represent rational polytherapy*

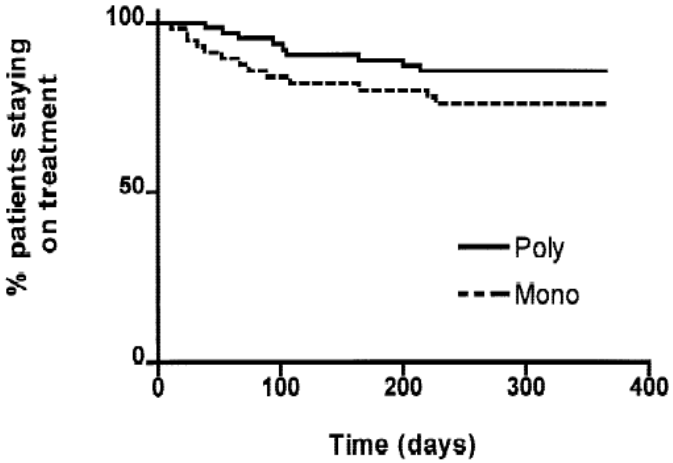
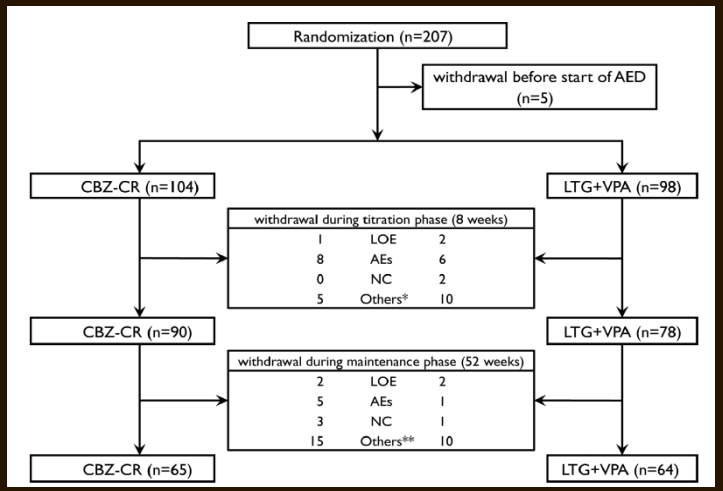
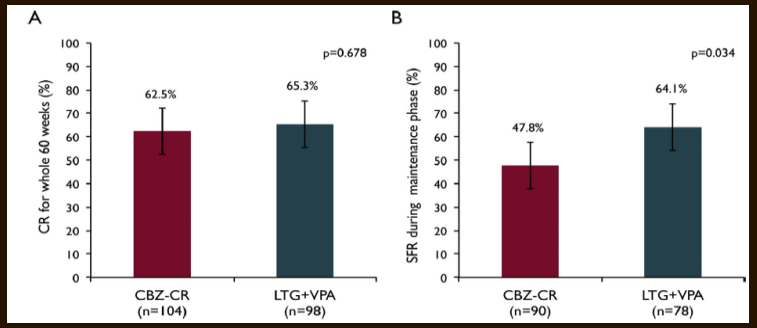


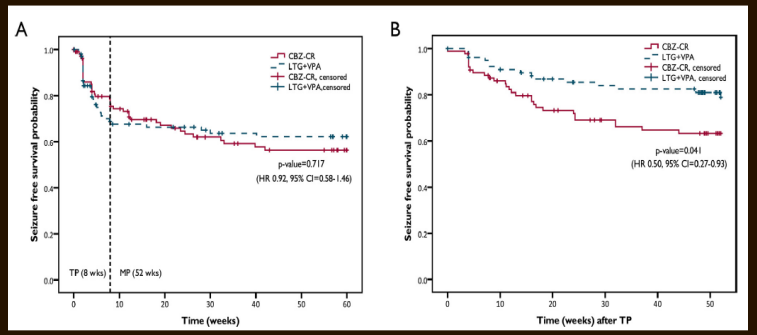
FIG. 2. Survival curve for patients staying on treatment.

Monothrapy vs. Polytherapy
- Korean Open Randomized Trial -

- CBZ-CR vs. LTG+VPA Comparative Study in Newly Diagnosed Partial Epilepsy
  (Lee BI et al. Seizure 2018; 55:17-24)
  - N=202(CBZ-CR in 104 and 98 in LTG+VPA)
    - T.P.= 8 weeks: CBZ-CR 300mg bid vs. LTG75mg+VPA500mg #1 (TDL: 0.6 vs. 0.58)
    - M.P= 52 weeks: max. dose: CBZ-CR=1200mg/day vs. LTG200mg+VPA 500mg/day
  - RESULTs
    - Completion rate for whole 60 weeks: 63.5% in CBZ-CR vs. 65.3% in LTG+VPA (P=0.68)
    - Seizure free rate for 52 weeks of MP: 47.8% in CBZ-CR vs. 64.1% in LTG+VPA(P=0.034)
  - **Conclusion:** LTG+VPA is a viable option as the initial drug regimen in newly diagnosed partial epilepsy







II. Era of New AEDs: 3.Revival of Polytherapy

Controversies about Monotherapy vs. Polytherapy

- SUMMARY -

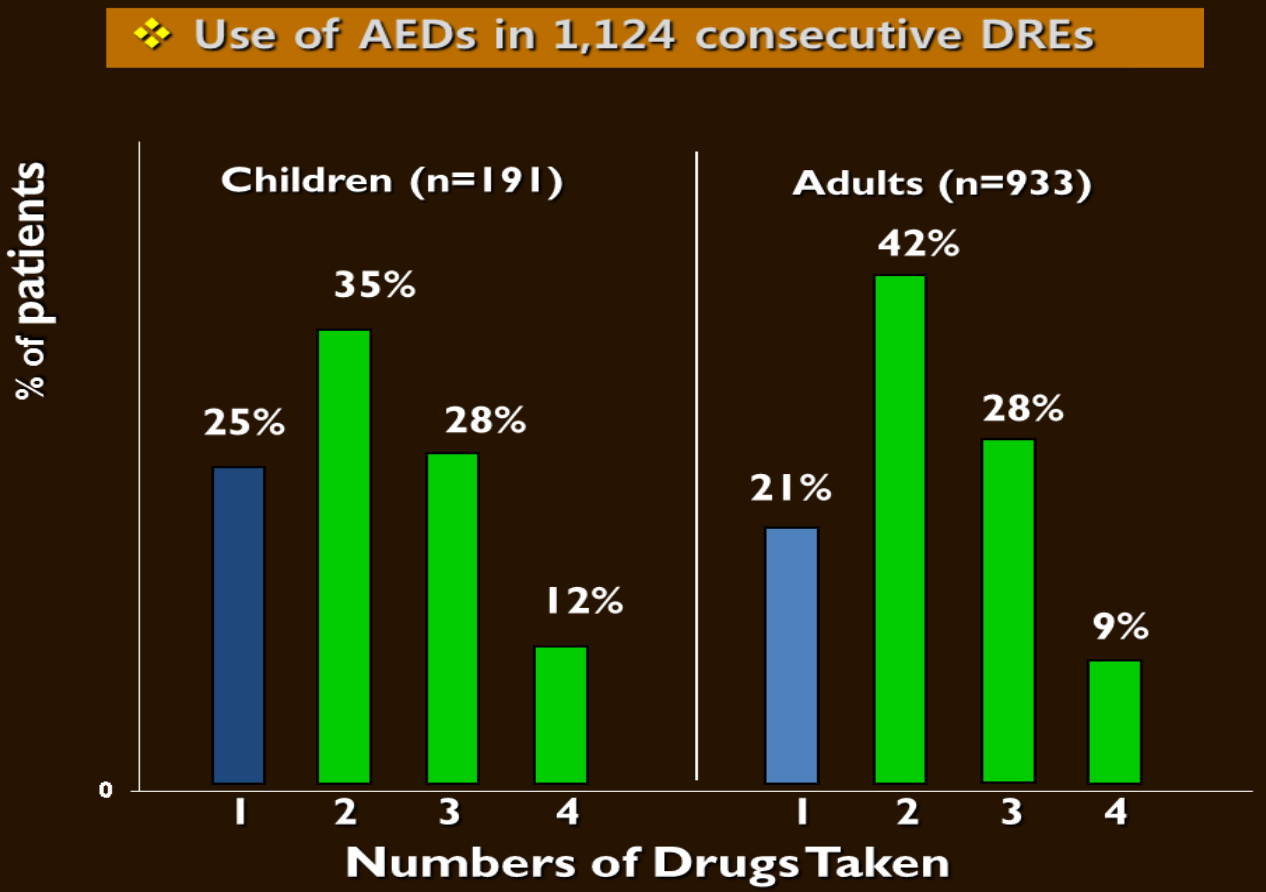
- The controversies have been continuing due to Lack of Class-I comparative data of the monotherapy with the polytherapy
- The concept of "Total Drug Load" has shown that Polytherapy is better tolerable than monotherapy if patients are taking a same TDL
- Previous concepts of Monotherapy being preferred to Polytherapy is not evidence-based
- Most important, but neglected factor was the adoption of "***specific polytherapy regimen***" to compare with monotherapy
  - With 25 AEDs available to use:
    → 300 regimens for duotherapy and 2300 regimens for triple therapy
    → Each polytherapy regimen may be different in efficacy and/or tolerability
    → Class-3 evidence of superiority of LTG+VPA to CBZ-CR as the first drug regimen
  - At present, choosing the best combination regimen is the major commitment of Epileptologists for the optimal care of patients with DREs

II. New Drug Era: (3) Revival of Polytherapy

When Should We Try Polytherapy?

- **Italian Multicenter Study** (Canevini MP et al. Epilepsia 2010; 51: 921)

  - ***Polytherapy is the Major Mode of Therapy in Patients with DREs***



II. Era of New AEDs: (3) Revival of Polytherapy
When Should We Try Polytherapy?

- **Systematic Drug Trials**
  - **Initial Drug Regimen:** *Monotherapy is the Rule*
  - **After Failure of the First Drug:** *Most Controversial Issue*

❖ **Faught and French** (Epilepsia 2009)

Add
Inadequate control with two sequential monotherapies

Patient tolerating first AED

First AED appropriate, provided partial control especially in the case with a high pretreatment seizure density and demonstrable underlying pathology

No anticipated drug interactions

Patient risk-averse, or consequences of seizure exacerbation are high

Switch
Patient failed a single monotherapy at adequate doses

Patient not tolerating first AED

First AED has disadvantages(e.g., frequent monitoring, high cost, known teratogenicity in woman of childbearing age), or pregnancy is anticipated

Drug interactions expected

Seizure exacerbation not likely

❖ If the first drug failed due to LOE, add-on therapy of second drug is preferred
(BW Abou-Khalil, 2019; Continuum)

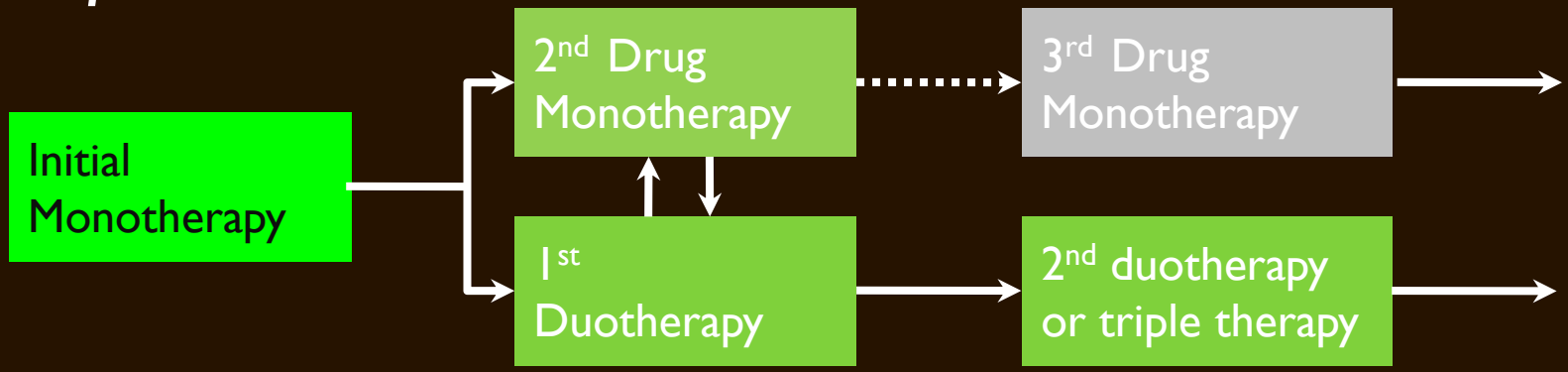
II. Era of New AEDs: (3) Revival of Polytherapy

When Should We Try Polytherapy?

- Increasing Trend for Earlier and Wider Use of Combination Therapy

  - ***Era of Conventional AEDs***

  - ***Era of New AEDs***



- Starting from 2016, FDA have approved AEDs (BRV, PER and Cannabinoids) for monotherapy based on the data from Adjunctive Therapy Trials, Why?

  → **Discrimination of Monotherapy vs. Polytherapy being attenuated ?**

III. Polytherapy in Real World Practice

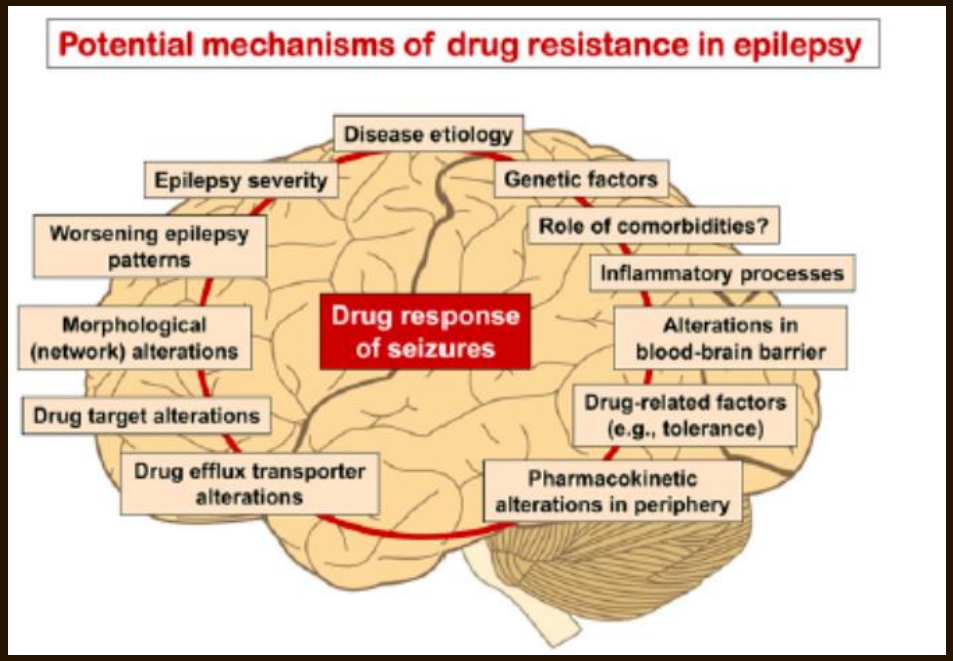
Why Polytherapy?

- Potential benefits from synergistic effect based on MOAs
- Patients may tolerate them better than higher dose of monotherapy when moderate dosages are used.
- May lessen the risk of seizure worsening related to the withdrawal of the First drug, which is partially effective.
  - *Cost of having more seizures are more expensive than medication costs.*
  - *If combination works, it would be more risky to convert to monotherapy.*
- If DRE is the result of complex interplay of diverse Mechanisms, Combination of have drugs having different MOA may have better chance of working

III. Polytherapy in Real World Practice

Why Polytherapy ?

- **Pathogenesis of DREs? Largely Unknown, however, considered " complex interplay of multiple pathomechanisms "**



It is difficult to expect to correct the problems by a single drug in DREs.

Wolfgang Löscher, et al. Pharmacol Rev 2020; 72:606–638

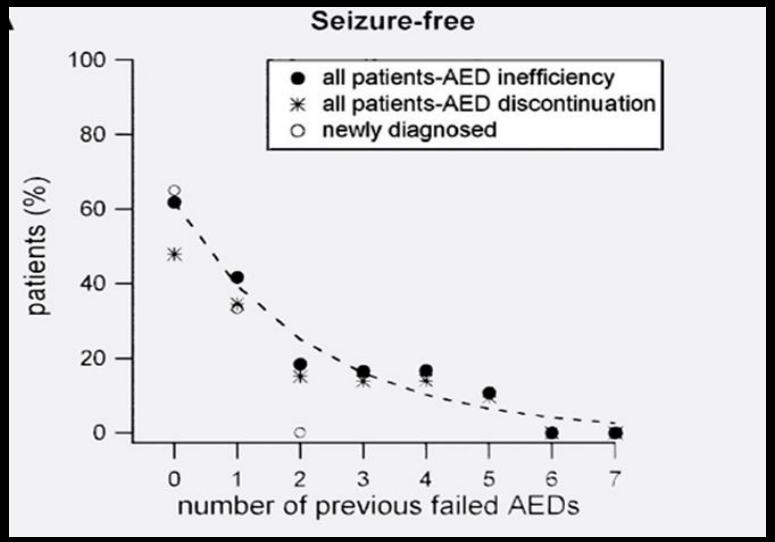
III. Polytherapy in Real World Practice
- *Outcome of Drug Trials in Patients with DREs* -

- Luciano and Shorvon (Ann Neurol 2007;62:375-381)
  - 265 trials of add-on of new AEDs in 155 patients
  - DRE: ≥1 Sz/mo, Sz duration≥5yrs, mean F/U:18.3mo
  - SF in 28% of all pts(n=155) or 16% of each drug introduction (n=265)
  - Favorable Factors: Previous trials of < 5 drugs (24% vs. 11%, P=0.001),
    idiopathic epilepsy (27% vs. 18%, P=0.017)
    shorter duration <10 years(30% vs 12%, P=0.01)

- Callaghan et al. (Epilepsia 2011;52:619-626)
  - 246 pts, ≥1 Sz/mo, failure to≥2AEDs, med F/U:5.9yrs
  - SFR in 33.4% at 7yrs of F/U (~5%/YR)
  - Relapse after remission in 34 of 59 patients (68%)

- Choi et al (Epilepsy Res 2011;93:115-119)
  - n=187 pts, ≥1Sz/mo, failure to ≥2AEDs, med F/U:7yrs
  - SFR in 13% (25pts) at mean F/U of 5.9yrs (~4%/yr)
  - Relapse after remission in 15 pts (60%)

- Schiller and Najjar (Neurology, 2008)
  - SFR in Sequential Drug Trial
    - 61.8% to first drug
    - 41.7% after failure of 1st drug
    - 16% after failure of 2nd to 5th drugs
    - 0% after failure of 6th drugs



III. Polytherapy in Real World Practice

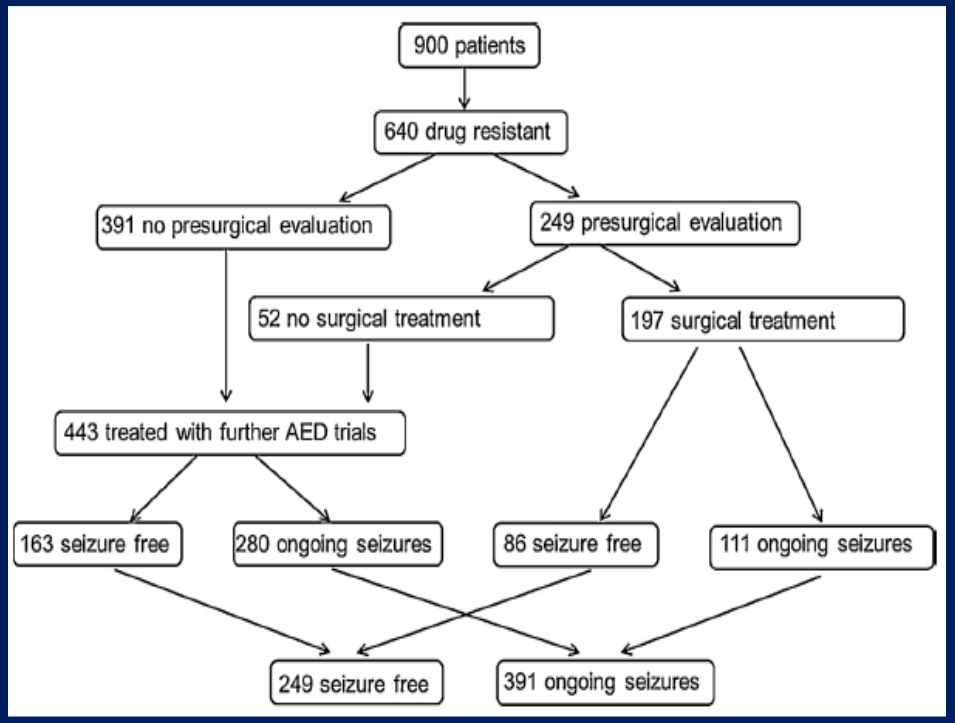
Trajectory of incident Cases of DRE satisfying ILAE-Criteria

- **Choi et al.** *(Epilepsia 2016;doi:10.1111/epi.13406)*
  - N=403 adults who failed to 2 AEDs due to inefficacy and starting their 3rd AED
  - At FU of 65 months: 53% did not achieve 1-YR
    16% had alternating periods of remission and relapses
    - 16% achieved early Terminal Remission(within 1 year)
    - 15% achieved delayed Terminal Remission(after 1 year)
  - Predictive Factors for Seizure Remission
    - Epilepsy Type: OLE(38%), Genetic generalized(44%), Unknown(45%)
      vs. TLE(25%) or Encephalopathic Epilepsy(7%)
    - Periods of FU: the longer FU, the more likely patients express better trajectory
    - Symptomatic vs. cryptogenic etiology: 25% vs. 37% , not significant

III. Polytherapy in Real World Practice

Long-term Seizure Outcomes

- **F Conte et al**(Seizure 2018;62: 74–78)
  - N= 640: failed to ≥ 3 AEDs
    - mean age at onset: 20.5 (±16.6) years
    - mean disease duration: **23.9(±15.6)** years
    - mean No of AED trials was 6.3 (± 3.2)
    - **512(80.0%)** were FE,
      66(10.3%) :GE, and 62(9.7%): UD
    - Structural lesions in **314 (61%)** patients
  - N=249(38.9%): Presurgical evaluation
    - N=197(30.8%): Surgery
      → 139 resective surgery,
      46 VNS, 9 radiosurgery, 4 DBS
      → 86 (**53.2% of Resective Surgery**)were
    - N= **443(69.2%):** further AED trials, → 163 (**36.8%**): SZ Free
  - Despite the availability of a wide variety of pharmacological and surgical treatments, over 60% of patients are not rendered seizure free.



III. Polytherapy in Real World Practice

Which Drugs for Polytherapy ?

- ***Features of Ideal AED Combination***

  - No pharmacokinetic interactions
  - Positive(or Synergistic) Pharmacodynamic Interaction
    - Supra - additive efficacy
    - Infra - additive toxicity
  - Avoid drugs having same AEs profile

Improve Therapeutic Index

III. Polytherapy in Real World Practice

- **Rational Polytherapy**
  - **Hypothesis and/or Experience driven Approach**
  - **Combining Drugs based on the Ideal combination Principle**
    - No pharmacokinetic interactions
    - Positive(or Synergistic) Pharmacodynamic Interaction
      - Supra - additive efficacy
      - Infra - additive toxicity
    - Avoid drugs having same AEs profile
    - Prefer drugs having a high Therapeutic Index
  - **Appropriate Drugs for the Seizure Types and Epilepsy Syndromes**
  - **Appropriate Drugs for the patient's comorbidities and concomitant drugs**

III. Polytherapy in Real World Practice
- Rational Polytherapy -

- ***How to choose Drugs?*** Two Step Approaches

Step 1. Listing of Candidate drugs for combination in a given clinical scenario	Step 2. Selecting a drug best matching to the first drug
Drugs without previous exposure	Drug having different MOA
Drugs found effective in previous exposure	Drug having less or no pharmacokinetic interactions
Drugs being effective in given SZ types of Epilepsy Syndrome	Drugs having different side effects profiles
Drugs not enzyme inducing	Drugs fitting to one of known combination regimens carrying synergistic interactions
Drugs having higher therapeutic effects (better safety and/or tolerability)	Drugs being effective in patient's comorbidities

- 35 year-old male with focal epilepsy of unknown etiology having depression, who failed to control Seizures to initial monotherapy of CBZ-CR
  - Candidate AEDs to consider as second drug: First-line drugs for focal seizures
  - NICE: PHT, VPA, LTG, OXC
  - AAN/AES: LTG, LEV, ZNS, LMC (GBP and TPM has changed to level U in 2018)

First Step	Previous Exposure	Effective in previous exposure	Effective in SZ types	Enzyme inducer	Safey/ tolerability
PHT	none	NA	Yes	Yes	+/-
VPA	none	NA	Yes	No	+
LEV	none	NA	Yes	No	+
LTG	none	NA	Yes	No	+
ZNS	none	NA	Yes	No	+
LCM	none	NA	Yes	No	+

Second Step	MOA	PK-Drug interaction	Side effects	Synergistic combination	Comorbiditis (depression)	Total
PHT	- 1(Na+ channel)	- 1(Y)	- 1(S)	-1(A)	0 (±)	- 4
VPA	+1(multiple action)	- 1(Y)	+1(D)	0(N)	+1 (P)	+3
LEV	+1(SV2A modulate)	+1(N)	+1(D)	+1(S)	-1(N)	+3
LTG	0 (Na+channel plus)	0(±)	-1(S)	-1(A)	+1(P)	- 2
ZNS	0 (Na+channel plus)	0(±)	+1(D)	0(N)	-1(N)	0
LCM	0 (Na+chann. slow inactivation)	+1(N)	-1(S)	-1(A)	0(±)	- 1

CASE (CHJ, 39 y.o. M)

CC: recurrent LOC despite AEDs therapy

Onset: GTCS at 2004 (at 25 y.o.), which were treated in a few referral centers

Seizure Types:

- Auras only: heat sensation in the retroauricular area, tinnitus, hearing difficulties, palpitations and nausea lasting for 30 seconds --------- 2/week
- CPS: motionless staring, unresponsive and does not recall the events------- 2/ month
- GTCS: None during the past 10 years(since start AEDs therapy)

AEDs at the initial visit :LEV250 bid, - PDD/DDD= 500/1500: 0.33

OXC 900 bid , - 1800/1000=1.8

PER 2mg q hs. 2.0/8.0 = 0.25

VPA 300mg bid 600/1500=0.4 ------ PDD/DDD=2.8

PH and FH= Negative

Comorbidities: None

N/E: Negative

EEG: biT independent polymorphic delta slow with superimposed SWs

MRI: Negative

Self report survey: GAD=11/24, NDDIE=18/24 and LAEP=66/76

IMP; Cryptogenic TLE, which is DRE

CASE 1. (CHJ, 39 y.o. M) 0697905

Assessment: Cryptogenic TLE, which is DRE

Polytherapy with evidence of Drug Toxicity (LAEP=66/76), *largely due to high dose OXC (PDD/DDD=1.8)*

OXC: not effective

Comorbidity= depressive mood

Plan; Switch of OXC to LTG + VPA combination(VPA will be added later than LTG)

increase LEV to minimal therapeutic dose; 500mg bid

increase FYC to minimal therapeutic dose; 4mg/day

if SZ recur, add on LCM: slow inactivation of Na channel being effective to FSz, no PK interactions

if SZ recur, add on ZNS: different MOA, no PK- interactions evidence of synergistic interactions with PER

AEDs at 4 mo FU :

LEV:500mg bid + LCM 50mg bid +LTG 100mg bid + TRL 150mg bid + VPA 250mg bid + FYC 4mg/day

PDD/DDD=0.33+ 0.33+ 0.66+ 0.3+ 0.33+ 0.5= 2.5 (decreased from 2.8)

At 1st visit: GAD=11/24, NDDIE=18/24, LAEP=66/76

At 4 mo of FU: GAD= 5/21, NDDIE=10/24, LAEP=46/76

SZ improvement: aura only: 2/week to 1/week and no CPS(2/mo to none)

Future Plan; d/c TRL and if auras continue, consider add-on ZNS

III. Polytherapy in Real World Practice
- Conclusion -

- No Class I & II evidence supporting the "Concept of Rational Polytherapy" yet

- However
  - Experimental evidence have provided the "Concept of Mechanistic Combinations"
  - Clinical evidence for "Rational Polytherapy" coincides with animal experiment, at least partly
    - Combination of drugs having same mechanisms (e.g., sodium channel blockers) is associated higher rate of AEs and lower efficacy
    - Clinical experience of mechanistic combinations are generally favorable, among which LTG + VPA combination has the best clinical data of synergism

- "Rational Polytherapy" is still an Art than Science, but the best Guideline for pharmacotherapy of DREs at present, continuous Drug Trials adopting its principle seem to work in a significant proportion of patients.

Thanks for Your Attention